

REMARKSI. Introduction

In response to the Office Action dated November 29, 2002, claims 1-18 (which are directed to a non-elected embodiment of the invention) have been cancelled and claims 19 and 21 have been amended. Claims 19-24 remain in the application. Re-examination and re-consideration of the application, as amended, is requested.

II. Claim Amendments

Applicants' attorney has made amendments to the claims as indicated above. These amendments were made solely for the purpose of clarifying the language of the claims, and were not required for patentability or to distinguish the claims over the prior art.

III. Non-Art Rejections

On page 3 of the Office Action, claims 19-24 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

Applicants' Attorney first wishes to thank Examiner Lukton for his very helpful suggestions regarding clarifying language for the claims. In this context, claim 19 has been amended hereinabove in accordance with the Examiner's suggestions in order to clarify the claims language. Applicants note that the amendments to claim 19 are merely clarifying and introduce no new matter. A method of inhibiting aggregation of a peptide is generally discussed for example in the first paragraph of the summary, page 2, lines 13-21; the full name tris(hydroxymethyl)aminomethane is generally discussed for example in the first paragraph on page 7, lines 1-4, the mitigation of the effect that carbonic acid (aqueous carbon dioxide solutions exhibit the equilibrium  $\text{CO}_2 + \text{H}_2\text{O} \rightleftharpoons \text{H}_2\text{CO}_3 \rightleftharpoons \text{H}^+ + \text{HCO}_3^-$ ) has on the pH of polypeptide formulations is generally discussed for example in the third paragraph of page 5, lines 18-27; and the use of such buffers for a time and under conditions effective to inhibit aggregation is generally discussed for example on page 6, lines 17-26.

As Applicants have clarified the language of the claims in exact accordance with the Examiner's suggestions, the withdrawal of the rejection under 35 U.S.C. §112, second paragraph is respectfully requested.

#### IV. Prior Art Rejections

On page 4 of the Office Action, claims 19-21 and 23-24 were rejected under 35 U.S.C. §103 as being unpatentable over Massey et al., U.S. Patent No. 4,839,341 (Massey). On page 4 of the Office Action, claim 19 is rejected under 35 U.S.C. §103 as being unpatentable over Langballe et al., U.S. Patent No. 6,174,856 (Langballe).

The following sections respond to each of the Examiner's rejections under 35 U.S.C. §103.

##### A. Subject Matter of the Claimed Invention.

Independent claim 19 is directed to methods of inhibiting aggregation of a polypeptide by combining the polypeptide with a buffer containing both TRIS and a second buffering molecule selected so that it does not contain a free amine group and which mitigates the change in pH that results from the formation of carbonic acid. As noted for example at page 10, lines 25-29, the use of buffering molecules that do not contain a free amine group are preferred embodiments of the invention due to the decreased chemical reactivity of such molecules.

##### B. Response to Examiner's rejection under 35 U.S.C. §103 in view of U.S. Patent No. 4,839,341.

Applicants respectfully traverse the rejection in view of Massey because this reference fails to teach or suggest buffer systems which combine TRIS and a second buffering molecule having the specific characteristics recited in the claims (e.g. no free amine group). In particular, while Massey recites a number of different buffering molecules that are commonly used in polypeptide formulations, this reference fails to discuss any of the chemical characteristics of these molecules, much less the presence or absence of free amine groups.

Massey not only fails to teach or suggest methods utilizing buffering molecules lacking a free amine group but further teaches away from the claimed invention by teaching artisans that "the

preferred buffers are TRIS and glycinamide", a molecule which, as shown by the chemical formula provided herein as Exhibit A, contains a free amine group (see e.g. Massey, column 4, lines 40-41). Therefore, after reading this reference as a whole (as required by M.P.E.P. 2141.02), Applicants respectfully disagree with the Examiner's assertion that their methods that utilize TRIS combined with molecules lacking a free amine group are obvious in view of Massey's explicit teaching to the contrary, i.e. that it is preferable to inhibit the aggregation of polypeptides using formulations that include buffering molecules having free amine groups.

As noted above, Massey fails to teach or suggest selecting TRIS out of the list of buffering molecules recited in this reference and then combining this molecule with a second molecule that is further selected to: (1) lack a free amine group; and (2) function to mitigate the change in pH that results from the formation of carbonic acid. Moreover, Massey teaches away from the claimed invention by informing artisans that preferred buffers are TRIS and glycinamide, a molecule which actually contains a free amine group. Consequently, one skilled in the art could not have found the claimed invention obvious in view of this reference. For these reasons, Applicants respectfully request the withdrawal of the rejection under 35 U.S.C. §103 in view of U.S. Patent No. 4,839,341.

C. Response to Examiner's rejection under 35 U.S.C. §103 in view of U.S. Patent No. 6,174,856.

Applicants respectfully traverse the rejection in view of Langballe because this reference fails to teach or suggest buffer systems which combine TRIS and a second buffering molecule having the specific characteristics recited in the claims (e.g. no free amine group). In particular, while Massey recites a number of different buffering molecules that are commonly used in polypeptide formulations, this reference fails to discuss any of the chemical characteristics of these molecules, much less the presence or absence of free amine groups.

Langballe not only fails to teach or suggest methods utilizing buffering molecules lacking a free amine group but further teaches away from the claimed invention by teaching artisans that "[i]t has now surprisingly been found that the stability of insulin compositions can be significantly improved by formulating the compositions using a combination of a buffer such as glycylglycine (Gly-Gly) and metal ions such as  $Ca^{++}$ . It has in particular been found that when the sodium

phosphate buffer in a traditional insulin composition is replaced with a Gly--Gly buffer in combination with calcium ions, the formation of soluble aggregates during storage at 5° C. decreased remarkably" (column 3, lines 28-36). In particular, glycylglycine is a molecule which, as shown by the chemical formula provided herein as Exhibit B, contains a free amine group. Therefore, after reading this reference as a whole (as required by M.P.E.P. 2141.02), Applicants respectfully disagree with the Examiner's assertion that their methods that utilize TRIS combined with molecules lacking a free amine group are obvious in view of Langballe's explicit teaching to the contrary, i.e. that it is preferable to inhibit the aggregation of polypeptides using formulations that include buffering molecules having free amine groups.

As noted above, Langballe fails to teach or suggest selecting TRIS out of the variety of buffering molecules recited therein and then selectively combining this molecule with a second molecule that is further selected to: (1) lack a free amine group; and (2) function to mitigate the change in pH that results from the formation of carbonic acid. Moreover, Langballe teaches that preferred buffers contain glycylglycine, a molecule which actually contains a free amine group. Consequently, one skilled in the art could not have found the claimed invention obvious in view of this reference. For these reasons, Applicants respectfully request the withdrawal of the rejection under 35 U.S.C. §103 in view of U.S. Patent No. 6,174,856.

#### V. Conclusion

Thus, Applicants submit that independent claim 19 is allowable over Massey and Langballe. Further, dependent claims 20-24 are submitted to be allowable over Massey and Langballe in the same manner, because they are dependent on independent claim 19, respectively, and thus contain all the limitations of the independent claims. In addition, dependent claims 20-24 recite additional novel elements not shown by Massey and Langballe.

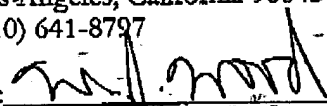
In view of the above, it is submitted that this application is now in good order for allowance and such allowance is respectfully solicited. Should the Examiner believe minor matters still remain that can be resolved in a telephone interview, the Examiner is urged to call Applicants' undersigned attorney.

Respectfully submitted,

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